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Review Article

Hemophagocytic Lymphohistiocytosis: A Life Threatening Cytopenic Condition

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Abstract:

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening disorder that occurs in many underlying conditions in all age. This is characterized by unbridled activation of cytotoxic T lymphocytes, natural killer (NK) cells and macrophages resulting in raised cytokine level. Those cytokines and immune mediated injury occur in multiple organ systems. It may be primary and secondary. Primary HLH is familial, childhood presentation and associated with gene mutations. Secondary HLH is acquired, adulthood presentation that occurs in infections, malignancies inflammatory and autoimmune diseases etc. Clinical manifestations include fever, splenomegaly, lymphadenopathy, neurologic dysfunction, coagulopathy, features of sepsis etc. Laboratory investigation includes cytopenias, hypertriglyceridemia, hyperferritinemia, abnormal liver function, hemophagocytosis, and diminished NKcell activity. Treatment modalities include immunosuppressive, immunomodulatory agents, cytostatic drugs, T-cell antibodies, anticytokine agents and hematopoietic stem cell transplantation (HSCT). Besides those, aggressive supportive care combined with specific treatment of the precipitating factor can produce better outcome. With treatment more than 50% of children who undergo transplant survive, but adults have quite poor outcomes even with aggressive management.

Key words: Hemophagocytic lymphohistiocytosis (HLH), Hepatosplenomegaly, Cytopenias.

Introduction:

HLH is not an independent disease but rather a life-threatening clinical syndrome that occurs in many underlying conditions and in all age groups. This is the consequence of a severe, uncontrolled hyperinflammatory reaction with high mortality even with appropriate treatment[1].

Epidemiology:

HLH, initially named histiocytic medullary reticulosis, was first reported in the literature in 1939 by Scott & Robb-Smith who described a child as having a neoplastic histiocytic disorder[2]. A retrospective series from a large academic hospital in Texas suggested a prevalence of HLH in Texas of 1 in 100,000 children, with a median age at diagnosis of 1.8 years[3]. A review of multiple patient cohorts suggests an average age at presentation of approximately 50 years, when occurs in adulthood[4,5]. In case of adult incidence of HLH, it has been estimated to account for as many as 1 out of every 2,000 adult admissions at tertiary medical centers[6]. The sex ratio in children appears to be close to 1:1[7]. In adults, there may be a slight male predominance[4]. It has been demonstrated, however, that certain subtypes of familial HLH are more commonin certain ethnic or national groups[8]. A seasonal pattern has been suggested in which cases may occur more often in the summer[9].

Pathogenesis:

HLH is characterized by an unchecked and persistent activation of cytotoxic T lymphocytes and NK cells. Failure to control the immune response leads to increased secretion of inflammatory cytokines and macrophage activation, causing systemic inflammatory symptoms and signs. The magnitude of pathologic inflammation produces potentially life threatening immune mediated injury of multiple organs. HLH is often classified as primary or familial (occurring in the presence of an underlying predisposing genetic

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defect in immune function) or as secondary or reactive (occurring in the absence of an underlying predisposing defect, typically in the setting of an infectious, malignant or autoimmune trigger). Infection is usually associated with HLH and acts as common precipitant or triggering factor. Commonest is the viral infection (Herpes viruses especially EBV, Cytomegalovirus, Varicella-zoster virus, Human immunodeficiency virus, Adenovirus, Influenza A, Hepatitis C virus, Hepatitis B virus, Roseolo virus etc.), then bacterial infection (Sepsis, Typhoid fever, Tuberculosis, Rickettsia, Helicobacter pylori, Morganella spp, Staphylococcus epidermidis, Klebsiella spp, Clostridium difficile, Mycobacterium tuberculosis, Streptococcus pneumoniae, Aspergillus spp and Babesia microti), protozoa (Leishmania, Plasmodium) and fungi (Histoplasma) infection. Malignancies (Lymphoma, Solid tumour, Hematologic malignancy and Polycythemia vera or Myelodysplastic syndrome etc.) are the most common trigger for the development of HLH in adults. Secondary HLH occurs in the setting of rheumatologic disease that most commonly seen in patients with Juvenile idiopathic arthritis, adultonset Still disease, Systemic lupus erythematosus and Kawasaki disease. HLH is also associated with immunosuppression, HSCT, organ transplantation and metabolic diseases[10,11].

Clinical features:

Patients with HLH frequently present with a constellation of signs and symptoms that include some combination of fever, organomegaly (lymphadenopathy, hepatomegaly and splenomegaly), neurologic dysfunction (such as encephalitis, seizures, or coma), edema, dermatologic manifestations, and stigmata of liver dysfunction or coagulopathy (such as jaundice or bruising). Patients are often critically ill and rapidly progress toward a septic shock-like clinical picture. Some differences may occur in the presentation of HLH between pediatric and adult populations. For example, hepatomegaly occurs in 95% of children but only 18-67% of adults[12].

Laboratory investigations:

The most prominent laboratory abnormality is cytopenias, which may be profound. Serum chemistry findings may suggest hemolysis, with hyperbilirubinemia and elevation of lactate dehydrogenase. Most patients have hypertriglyceridemia and marked elevation of ferritin[13]. Serum fibrinogen is typically low, and there may be disseminated intravascular coagulation[14]. Elevated circulating fibrin degradation products and serum ferritin in patients with HLH appear to be associated with increased risk for death[15]. Histopathologically, hemophagocytosis is seen in bone marrow, spleen, and lymph nodes[16,17] and occasionally the central nervous system[18] and skin[19]. Activated macrophages may engulf erythrocytes, leukocytes, and platelets, their precursors, and cellular fragments. These cells appear "stuffed" with other blood cells. Hemophagocytosis may be present in the liver, but infiltration of the hepatic portal tracts with lymphocytes is also common[16,17]. Reduced NK cell activity may be seen in HLH as a reflection of an underlying immune defect[20]. Dramatically elevated levels of sIL2Ra (also known as soluble CD25) appear to be relatively specific for HLH[21]. A relatively high soluble CD25/ferritin ratio is useful in the differentiation of lymphoma-associated HLH from so-called benign HLH (nonmalignant etiologies of HLH)[22].

Diagnosis:

Timely diagnosis of HLH is of special importance, as patients may be critically ill and delays in diagnosis may result in poor outcomes. Diagnosis is based on clinical criteria, and no single diagnostic laboratory assay or pathognomonic clinical finding exists that can establish a diagnosis. The most commonly used and widely accepted diagnostic criteria for HLH are the HLH-2004 criteria (Table-I) from the Histiocyte Society. HLH diagnosis can be established by fulfilling five of the following eight proposed criteria[1,11.26].

Table-I: HLH-2004 criteria.

1. Fever 2. Splenomegaly 3. Cytopenias affecting ≥ 2 lineages Hemoglobin <90 g/L (below 4 weeks of age, <100 g/L) Platelet count $<100\times10^9$/L Absolute neutrophil count $<1\times10^9$/L 4. Hypertriglyceridemia and/or hypofibrinogenemia Triglycerides ≥ 265 mg/dL(≥ 3 mmol/L) Fibrinogen ≤150 mg/dL 5. Hemophagocytosis in bone marrow, spleen or lymph nodes, (CSF). 6. Low or absent NK cell activity 7. Ferritin ≥ 500 µg/L 8. sCD25 (sIL2Ra) ≥ 2,400 U/ml
Supportive evidence is cerebral symptoms with moderate pleocytosis and/or elevated protein, elevated transaminases, bilirubin, and lactate dehydrogenase.

Another HLH Score was published in 2014. That has nine criteria (the presence ofimmunosuppression, fever, organomegaly; elevations in triglyceride levels, ferritin levels, aspartate aminotransferase/serum glutamic oxaloacetic transaminase levels, and fibrinogen levels; and the presence of cytopenias and hemophagocytosis

on bone marrow aspirate). Other diagnostic scoring systems and criteria have been examined for certain HLH populations (e.g., Macrophage activation syndrome), but none has gained widespread acceptance[23].

Management:

General consideration:

Treating HLH is challenging. The treatment varies depending on the underlying disease and severity of symptoms. Hyperinflammation has to be suppressed to prevent or treat the deleterious effects of hypercytokinemia, including coagulopathy, prolonged neutropenia, CNS hyperinflammation, and impending organ failure. Prolonged immuno suppressive treatment could not only lead to reactivation of the original trigger and of other dormant infectious agents, but also to an increased susceptibility toward a new triggering agent. Therefore, judicious use of available therapeutic agents is important. Assuming that the infection has to be treated first and only then HLH is adangerous misconception[1].

Because HLH is a syndrome of unbridled immune activation, the goal of therapy is to reverse the deleterious uncontrolled immune response[24].

Treatment trial:

The HLH-94 trial was the first international HLH clinical trial, and combined myelosuppressive/ cytotoxic treatment with epipodophyllotoxins with immunosuppressive therapy[25.] The HLH-2004 trial is the second international HLH study and successor to HLH-94, is currently on going[26].

Principles of treatment:

Principles of treatment is shown in Table-II. Although suppression of hyperinflammation usually requires immediate action and should not be postponed, the search for a treatable trigger is mandatory. Therapy of an infectious agent does not render anti-inflammatory treatment unnecessary (except in Leishmania associated HLH), but may contribute to a faster reduction of the antigenic burden. Corticosteroids are the most important anti-inflammatory drugs for HLH. Due to its better penetration into the CSF, dexamethas one may be superior. Less severe cases may do well with corticosteroids and immunomodulatory drugs such as cyclosporine A (CSA) or immunoglobulins; however, these patients have to be followed carefully. Lately anticytokine treatment has been used successfully[1].

Table-II: Principles of treatment in HLH.

Mechanism	Drugs
Suppression of hyperinflammation (immunosuppression, immunomodulation)	Corticosteroids, IV immunoglobulins, Cyclosporin-A, anticytokine agents.
Elimination of activated immune cells and (infected) APCs (CTLs, histiocytes)	Corticosteroids, etoposide, T-cell antibodies, (antithymocyteglobulin,alemtuzumab), rituximab
Elimination of trigger	Anti-infectious therapy
Supportive therapy (neutropenia, coagulopathy)	Antifungals, antibiotics, plasma
Replacement of defective immune system	Hematopoietic stem cell transplantation (HSCT)

Etoposide is an effective agent for monocytic and histiocytic diseases. The two HLH study protocols of the Histiocyte Society have used a combination of dexamethasone, etoposide, and CSA, followed by HSCT for familial disease[26,27]. In patients with EBV-associated HLH, the addition of rituximab seems to be a valuable adjunct to therapy[28].

Alemtuzumab, an antibody against CD52 that is present not only on T cells but also on histiocytes, has been shown to be beneficial in patients with refractory HLH[29]. Plasma exchange, a historical treatment for FHL, may still be of use for patients who do not respond to standard treatment[30].

In patients with genetic HLH, HSCT has to be performed to correct the immune defect. Results are equal with matched related or unrelated transplantations[31].

Newer agents:

The Janus kinase 1/2 inhibitor ruxolitinib, currently FDA approved in the United States for the treatment of primary myelofibrosis and polycythemia vera, has been examined in a murine model of HLH such positive results ofan off-the-shelf, currently available agent are encouraging because clinical trials could readily be undertaken in humans[32]. Emapalumab (NI-0501, Novimmune) is a fully human, high-affinity anti-IFN-Ɣ monoclonal antibody that binds to and neutralizes human IFN-Ɣ. In 2015, the first results from an open-label phase II study of emapalumab in 13 children with primary HLH were reported[33].

Prognosis:

Early studies of children with familial HLH demonstrated that the disease is almost uniformly fatal

without therapy[25]. Long-term follow-up from the HLH-94 trial demonstrated an estimated 5-year probability of survival of 54% with a median follow-up of 6.2 years. Factors in this trial that predicted poor prognosis included very young age at the start of therapy (41% survival at <6 months of age versus 65% survival at >6 months of age) and neurologic involvement (40% versus 67%)[27]. The most common late effects in HLH-94 trial survivors were neurologic (such as severe mental retardation, cranial nerve palsies, and epilepsy), occurring in 19% of all surviving patients and 31% of surviving familial HLH patients. Non-neurologic late effects, which occurred in 16% of patients, included nutritional problems, growth retardation, hypertension, impaired renal function, obstructive bronchiolitis, and hearing impairment[29]. In a large retrospective US cohort of 68 adults with HLH, 31% of patients were alive after 32.2 months of median follow-up; them edian overall survival was 4 months. Patients with malignancy-associated HLH had the worst prognosis, with amedian survival of 2.8 months (versus 10.7 months for those with non-malignancy associated disease). The median survival for patients receiving an allogeneic HSCT was 21.5 months[8].

Conclusion:

HLH is a dangerous life-threatening hyperinflammatory syndrome with nonspecific clinical presentation and laboratory findings. A high level of awareness is necessary to consider HLH in patients with prolonged fever, Hepatosplenomegaly, and cytopenias. Management of HLH remains difficult. Treatment can be life-saving but may interfere with immune functions that further, needs to manage the situation. This is challenging for clinician to suspect such a case as HLH from a vague clinical situation, then confirm it and treat accordingly to attain a good outcome.

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